# Best Practice

## EVIDENCE-BASED CASE REVIEW

# Diagnosis and treatment of deep vein thrombosis

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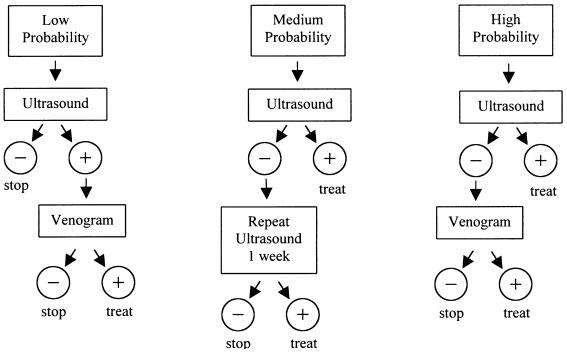
Ms Aviles, a 61-year-old moderately obese Ecuadoran woman with diabetes mellitus, osteoarthritis, and hypertension, saw her physician because for 3 days she had had pain and swelling in her left calf. She did not recall any trauma. On examination, her left calf diameter (measured 10 cm below the tibial tuberosity) was 3 cm larger than her right and was slightly tender to touch. She had bilateral varicose veins. The patient works as a housecleaner.




Diagnostic algorithm for evaluation of proximal deep venous thrombosis using ultrasonography and venography based on pretest probability.

## METHODS

### Searching the literature

For an introductory overview of the field, I searched OVID using the term "venous thrombosis." I limited the search to the subheadings "diagnosis," "local holdings," and "full text." Sixteen articles were found, of which 4 were recent review articles on deep venous thrombosis (DVT) in peer-reviewed journals.

Once I had formulated specific clinical questions, I searched OVID with the terms "venous thrombosis and thrombophilia" and "venous thrombosis/diagnosis and D-dimers." I chose studies that compared D-dimers with the venography, or less commonly, with an accepted diagnostic algorithm using ultrasonography.

### Appraising the literature

I excluded studies that were not blinded and those that did not have explicit diagnostic criteria for deep venous thrombosis.

## WHAT IS THE SIMPLEST AND MOST ACCURATE WAY TO DIAGNOSE DVT?

Clinical diagnosis is notoriously inaccurate for diagnosing DVT, although rules for making clinical predictions can be helpful. Table 1 demonstrates such a rule, developed by Wells and associates, that allows a determination of pretest probability.[1]

Based on the venography as a diagnostic standard—although magnetic resonance angiography has the potential to rival venography for accuracy—Doppler ultrasonography has a sensitivity and specificity of 95% for proximal DVTs (table 2). The ability to fully compress the popliteal and femoral veins with the ultrasound probe strongly excludes the diagnosis of DVT, and the lack of full compressibility strongly confirms the diagnosis. Doppler ultrasonography is more accurate for detecting symptomatic, proximal, and first-time DVTs than for detecting those that are asymptomatic, distal, or recurrent.[2]

Impedance plethysmography is less sensitive than Doppler ultrasonography.[3] D-Dimer assays have been developed to help rule out DVT. They have high sensitivity and negative predictive value but poor specificity.[4] A bed-

Table 1 *Clinical model for predicting pretest probability for DVT*

| Clinical feature | Score* |
|---|---|
| Active cancer within 6 mo | 1 |
| Paralysis, paresis, or cast of lower extremity | 1 |
| Recently bedridden >3 d or major surgery within 4 wk | 1 |
| Localized tenderness along distribution of deep vein system | 1 |
| Calf diameter >3 cm larger than opposite leg† | 1 |
| Pitting edema | 1 |
| Collateral superficial veins (nonvaricose) | 1 |
| Alternative diagnosis as likely or greater than that of DVT | −2 |

*Interpretation: 0 = low probability = 3% frequency of DVT; 1-2 = medium probability = 17% frequency of DVT; ≥3 = high probability = 75% frequency of DVT.
†Measured 10 cm below tibial tuberosity.

side version of this assay may turn out to be the simplest and fastest way to rule out DVT, but a positive result would require confirmation because many other conditions such as malignant neoplasms, disseminated intravascular coagulation, and hepatic failure may cause elevated D-dimer levels. There is still no consensus on the appropriate cutoff value for a negative D-dimer result, but it may lie between 500 and 750 ng per mL.[5,6] The lower the cutoff point, the more reliably a DVT can be ruled out with a negative D-dimer result, but at the cost of additional false-positive results.

The diagnostic approach to DVT evaluation can differ based on pretest probability,[7] as determined by clinical characteristics outlined earlier (table 1).[8] For a patient with a low pretest probability, a normal-appearing Doppler ultrasonogram would be sufficient to rule out a DVT, and the patient could be reassured. Abnormalities seen on ultrasonography (a positive result) would require venography for confirmation. Conversely, in a patient with a high pretest probability, a positive finding on ultrasonography would be sufficient to begin treatment and a normal ultrasonogram would require venography for confirmation.

For a patient with moderate probability, a positive result on Doppler ultrasonography would permit the initiation of treatment, but a negative result would require a follow-up ultrasonogram in 1 week. If the second ultrasonography was again normal, the patient could be reassured, but a "newly" positive result on ultrasonography would be an indication for treatment. If the initial ultrasonogram was normal, there is evidence to suggest that a negative D-dimer test result at that time might obviate the need to repeat the ultrasonography at 1 week.[9]

Ms Aviles' physician had a moderate clinical suspicion for DVT, and a Doppler ultrasonogram obtained that afternoon revealed a distal DVT. The patient wanted to know if she had to take a "blood thinner" for the blood clot in her leg.

## DOES EVERY PATIENT WITH DVT REQUIRE ANTICOAGULATION?

The main purpose of treating DVT is to prevent pulmonary embolism. Proximal DVTs (popliteal and higher) are associated with as high as a 50% incidence of pulmonary embolism if untreated[10]; therefore, anticoagulation should be instituted promptly. Distal DVTs propagate less than 20% of the time and usually do so within 1 week. Therefore, distal DVTs can be observed with serial ultrasonography (a second ultrasonogram 1 week later is usually sufficient), with treatment instituted only if proximal propagation is noted. The DVTs that remain confined to the calf are associated with a less than 1% risk of pulmonary embolism and a 2% chance of recurrent DVT.[11] If the results of the first ultrasonography are equivocal, however, or if they are normal in the face of a high clinical suspicion, venography should be performed.

Table 2 *Operating characteristics of diagnostic tests for proximal DVT**

| Diagnostic test | Sensitivity, % | Specificity, % | Positive LR | Negative LR |
|---|---|---|---|---|
| Venography | ~100 | ~100 | Infinity | 0 |
| Doppler ultrasonography | 95 | 95 | 19 | 0.05 |
| Duplex ultrasonography | 95 | 95 | 19 | 0.05 |
| Impedence plethysmography | 80 | 95 | 16 | 0.21 |
| Iodine 125 fibrinogen scan | 79 | 62 | 2.1 | 0.34 |
| D-Dimer level | 88-100 | 55-80 | 1.9-5.0 | 0.4-0.02 |

LR = likelihood ratio.
*From Black et al.[8]

## If it turned out that Ms Aviles had a proximal DVT, would she have to be admitted to the hospital, or could she be treated as an outpatient?

All patients with proximal DVT require some form of heparin therapy until the dose of sodium warfarin is therapeutic. This has traditionally been with intravenous unfractionated heparin, and this is still the standard of care. The use of low-molecular-weight (LMW) heparin, however, may allow certain patients to avoid hospitalization.

The LMW form of heparin is depolymerized from unfractionated heparin and has a more predictable anticoagulant effect, thus avoiding the need to assess prothrombin times. It also promotes less antibody formation and is associated with a lower risk of heparin-associated thrombocytopenia. Hemorrhagic side effects appear to be similar to those with standard heparin. At least 2 studies have shown that patients treated at home with LMW heparin plus warfarin compare favorably with those treated in the hospital with intravenous heparin plus warfarin. The incidence of the recurrence of thromboembolism was 6.9% versus 8.6% in 1 study[12] and 5.3% versus 6.7% in the other.[13] The incidence of major bleeding was similar (0.5% vs 2%, and 2% vs 1%). A recent Cochrane Library review concluded that LMW heparin was at least as effective as unfractionated heparin and that its use was associated with a lower incidence of major hemorrhage and decreased overall mortality.[14]

Candidates for home therapy must be able to learn to

self-administer subcutaneously and to understand when to call their physician for adverse events. Alternatively, arrangements can be made for daily nurse visits. The medical facility must have a system in place for nursing oversight, troubleshooting, and organized follow-up. In these situations, outpatient treatment of DVT is feasible, equally efficacious, and probably cost-effective.[15,16] In many cases, these requirements will be difficult to meet, and the patient will require admission to the hospital for either intravenous or LMW heparin. In all of these patients, warfarin therapy should be initiated on day 1. The heparin (intravenous or LMW) can be discontinued after at least 4 to 5 days and when the international normalized ratio is greater than 2.0 for 2 consecutive days.

## HOW LONG SHOULD ANTICOAGULATION LAST?

Two recent studies have led clinicians away from short courses of anticoagulation. In an open-label randomized trial, Schulman and colleagues compared 6 weeks with 6 months of warfarin therapy after a first DVT or pulmonary embolus.[17] Thromboembolic events recurred in 18.1% of the group receiving therapy for 6 weeks compared with 9.5% in the group treated for 6 months (absolute risk reduction [ARR] = 8.6%; number needed to treat [NNT] = 12). Kearon and associates conducted a randomized, double-blind trial of placebo versus warfarin after all participants had completed an initial 3-month course of anticoagulation.[18] The trial was halted at the 10-month interim analysis point because of a recurrence rate of 20.5% in the placebo group versus 1.3% in the group receiving extended warfarin (ARR = 19.2%, NNT = 5). Thus, for idiopathic first-episode DVT, anticoagulation should continue for at least 6 months. The optimal duration is unknown, although many clinicians cease treatment after 6 months.

The American College of Chest Physicians in the Fifth ACCP Consensus Conference on Antithrombotic Therapy admits that there is little solid evidence on which to base their duration guidelines for DVT in most clinical situations (table 3),[11] but they emphasize that age and prior thromboembolic events are powerful risk factors for recurrence.

Table 3 *Duration of anticoagulation for DVT**

| Episode of DVT | Cause | Duration |
|---|---|---|
| First | Reversible or time-limited risk factors—surgery, trauma, short-term immobility, estrogen replacement | 3-6 mo |
| First | Heterozygous factor V Leiden | 3-6 mo |
| First | Idiopathic | At least 6 mo |
| First | Malignancy (until resolved), *homozygous* factor V Leiden, antiphospholipid antibody (until resolved), deficiency of antithrombin III, protein C or S | 12 mo to lifetime |
| Recurrence | | Probably lifetime |

*Adapted from American College of Chest Physicians[11]

The physician sent Ms Aviles home with instructions to elevate the leg and take aspirin for pain. One week later, a second ultrasonogram showed no proximal extension of the clot. The physician prescribed support stockings for the varicose veins. She reassured Ms Aviles that the blood clot was unlikely to do serious harm, but she was unsure if she had to pursue an aggressive workup for thrombophilia or malignant neoplasm in this patient.

## WHEN IS A THROMBOPHILIA WORKUP WARRANTED?

Numerous studies have analyzed the frequencies of genetic thrombophilias, but they have differed in their study populations and, therefore, have reported widely discordant hazard ratios. Activated protein C resistance and prothrombin gene mutations appear to be the most common of these thrombophilias. Deficiencies of protein S, C, and antithrombin III and the presence of antiphospholipid antibodies are less common. Homozygosity for the factor V Leiden mutation appears to confer a greater risk than heterozygosity. At least 1 study found no increased risk of recurrent DVT in subjects who were heterozygous for factor V Leiden without any other coexisting genetic defects.[19]

Although the ACCP suggests a slightly longer anticoagulation period for patients with protein C, S, and antithrombin III deficiencies and patients homozygous for the factor V Leiden mutation, little data support this. The argument could be made that knowledge of these thrombophilias would not change management substantially. It is true that these thrombophilias are likely associated with an increased incidence of recurrence, but any patient with DVT is at risk for recurrence, and advice about surgery, pregnancy, oral contraceptives, and the like should be the same. Also, as much as 10% of the general population may possess 1 or more of these inherited thrombophilias,

so the clinical significance may be difficult to interpret.

A reasonable approach might be to institute a thrombophilia workup for younger patients (possibly <50 years) who have an episode of DVT in the absence of any risk factors, those with a family history of thromboembolic disease, or patients with a thrombosis of unusual location or severity and to prolong anticoagulation accordingly. This will miss a certain number of people whose DVT was precipitated by a known risk factor but who also have genetic thrombophilias.

## WHEN IS A WORKUP FOR MALIGNANT NEOPLASMS WARRANTED?

The yield of extensive evaluation for malignant lesions is low. In a population cohort in Denmark, it was found that 88 patients would have to be screened to uncover 1 excess cancer within the first year after DVT or pulmonary embolism.[20] Of cancers detected, 40% would already have metastasized. The strongest associations were with cancer of the pancreas, ovary, liver, and brain and in the first year only after the initial thromboembolic event. Another study that retrospectively analyzed patients younger than 40 years with DVT found no malignant neoplasms after a mean follow-up of 5 years.[21]

Beyond a thorough history and physical examination and age-appropriate cancer screening, there appears to be little utility in aggressive cancer workup after a first episode of DVT. Other secondary causes of DVT—nephrotic syndrome, congestive heart failure, myeloproliferative disorders—can usually be uncovered with the history, physical examination, and basic laboratory tests.

There was nothing in Ms Aviles' medical history to suggest cancer. There was no family history of clotting disorders. The physician performed a full physical examination, including breast and pelvic examinations, and ordered a mammogram and flexible sigmoidoscopy as part of regular screening. She told Ms Aviles that having 1 episode of DVT—even without knowing the cause—put her at risk for future DVTs and that she should be alert for situations that might provoke DVTs, such as immobilization, surgery, or estrogen therapy. She did not do a thrombophilia workup.

References


1 Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet* 1997;350:1795-1798.

2 Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. *Ann Intern Med* 1998;129:1044-1049.

3 Anderson DR, Lensing AW, Well PS, Levine MN, Weitz JJ, Hirsh J. Limitations of impedance plethysmography in the diagnosis of clinically suspected deep-vein thrombosis. *Ann Intern Med* 1993;118:25-30.

4 Kearon C, Julian JA, Newman TE, Ginsberg JS. Noninvasive diagnosis of deep venous thrombosis: McMaster Diagnostic Imaging Practice Guidelines Initiative. *Ann Intern Med* 1998;128:663-667 [published erratum appears in *Ann Intern Med* 1998;129:425].

5 Le Blanche AF, Siguret V, Settegrana C, et al. Ruling out acute deep vein thrombosis by ELISA plasma D-dimer assay versus ultrasound in inpatients more than 70 years old. *Angiology* 1999;50:873-882.

6 Watanabe R, Wada H, Mori Y, Nakasaki T, Sawa H, Shiku H. Plasma D-dimer levels in patients with deep vein thrombosis [in Japanese]. *Rinsho Byori* 1999;47:887-890.

7 Anand SS, Wells PS, Hunt D, Brill-Edwards P, Cook D, Ginsberg JS. Does this patient have deep vein thrombosis? *JAMA* 1998;279:1094-1099.

8 Black ER, Bordley DR, Tape TG, Panzer RJ. *Diagnostic Strategies for Common Medical Problems.* Philadelphia: American College of Physicians; 1999.

9 Bernardi E, Prandoni P, Lensing AW, et al. D-Dimer testing as an adjunct to ultrasonography in patients with clinically suspected deep vein thrombosis: prospective cohort study: The Multicentre Italian D-Dimer Ultrasound Study Investigators Group. *BMJ* 1998; 317:1037-1040.

10 Moser KM, LeMoine JR. Is embolic risk conditioned by location of deep venous thrombosis? *Ann Intern Med* 1981;94(pt 1):439-444.

11 Fifth ACCP Consensus Conference on Antithrombotic Therapy. *Chest* Suppl 1998;114:439S-769S.

12 Levine M, Gent M, Hirsh J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med* 1996;334:677-681.

13 Koopman MMW, Prandoni P, Piovella F, et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home: The Tasman Study Group. *N Engl J Med* 1996;334:682-687 [published erratum appears in *N Engl J Med* 1997;337:1251].

14 van den Belt AGM, Prins MH, Lensing AW, et al. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. In: Cochrane Peripheral Vascular Diseases Group, eds. *Cochrane Database of Systematic Reviews.* Cochrane Library [updated July 1, 1999].

15 Gould MK, Dembitzer AD, Sanders GD, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a cost-effective analysis. *Ann Intern Med* 1999;130:789-799.

16 Rodger M, Bredeson C, Wells PS, Beck J, Kearns B, Huebsch LB. Cost-effectiveness of low-molecular-weight heparin and unfractionated heparin in treatment of deep vein thrombosis. *CMAJ* 1998;159:931-938.

17 Schulman S, Rhedin AS, Lindmarker P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism: Duration of Anticoagulation Trial Study Group. *N Engl J Med* 1995;332:1661-1665.

18 Kearon C, Gent M, Hirsch J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999;340:901-907 [published erratum appears in *N Engl J Med* 1999;341:298].

19 De Stefano V, Martinelli I, Mannucci PM, et al. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. *N Engl J Med* 1999;341:801-806.

20 Sorensen HT, Mellenkjaer L, Steffensen FH, Olsen JH, Nielsen GL. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. *N Engl J Med* 1998;338:1169-1173.

21 Subira M, Mateo J, Souto JC, Altes A, Fontcuberta J. Lack of association between venous thrombosis and subsequent malignancy in a retrospective cohort study in young patients. *Am J Hematol* 1999;60:181-184.